# Pericardial Rather Than Epicardial Fat Is a Cardiometabolic Risk Marker: An MRI vs Echo Study

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*Background:* Several studies using echocardiography identified epicardial adipose tissue (EPI) as an important cardiometabolic risk marker. However, validation compared with magnetic resonance imaging (MRI) or computed tomography has not been performed. Moreover, pericardial adipose tissue (PERI) has recently been shown to have some correlation with cardiovascular disease risk factors. The aims of this study were to validate echocardiographic analyses compared with MRI and to evaluate which cardiac fat depot (EPI or PERI) is the most appropriate cardiovascular risk marker.

*Methods:* Forty-nine healthy subjects were studied (age range, 25–68 years; body mass index, 21–40 kg/m$^2$), and PERI and EPI fat depots were measured using echocardiography and MRI. Findings were correlated with MRI visceral fat and subcutaneous fat, blood pressure, insulin sensitivity, triglycerides, cholesterol, insulin, glucose, and 10-year coronary heart disease risk.

*Results:* Most cardiac fat was constituted by PERI (about 77%). PERI thickness by echocardiography was well correlated with MRI area ($r = 0.36$, $P = .009$), and independently of the technique used for quantification, PERI was correlated with body mass index, waist circumference, visceral fat, subcutaneous fat, blood pressure, insulin sensitivity, triglycerides, cholesterol, glucose, and coronary heart disease risk. On the contrary, EPI thicknesses correlated only with age did not correlate significantly with MRI EPI areas, which were found to correlate with age, body mass index, subcutaneous fat, and hip and waist circumferences.

*Conclusions:* Increased cardiac fat in the pericardial area is strongly associated with features of the metabolic syndrome, whereas no correlation was found with EPI, indicating that in clinical practice, PERI is a better cardiometabolic risk marker than EPI. (J Am Soc Echocardiogr 2011;■:■-■.)

*Keywords:* MRI, Echocardiography, Epicardial, Mediastinal and visceral fat

Several studies have shown that increased accumulation of fat around the heart is associated with an increased risk for cardiovascular disease and metabolic disease.[1-5] Cardiac fat can be distinguished in two depots: (1) epicardial adipose tissue (EPI), the fat concentrated in the atrioventricular and interventricular grooves, along the major branches of the coronary arteries and, to a lesser extent, around the atria, over the free wall of the right ventricle and over the apex of the left ventricle, and (2) pericardial adipose tissue (PERI), the fat situated on the external surface of the parietal pericardium within the mediastinum (alternatively termed mediastinal or intrathoracic fat).

Both EPI and PERI have been found to be strongly associated with obesity, preferential visceral fat accumulation, and hypertension.[2,5-9] In human hearts randomly collected from diagnostic autopsies, EPI was associated with body mass index (BMI), but it was not related to either hypertension or ischemia.[10] Recently, the $^1$H magnetic resonance spectroscopic technique has been used to study the intracellular lipid content of cardiomyocytes.[11] Visceral fat deposition has been recognized as an important risk factor for cardiovascular diseases[2,9] and is correlated with insulin resistance,[12,13] cardiovascular risk factors,[12,14] and the metabolic syndrome.[12]

Several techniques, including echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI), have been used to quantify fat deposition around the heart.[2,5,8,15,16] However, most published studies have used ultrasound and measured EPI thickness.[9,12,14,17,18] Recently, it has been demonstrated that EPI thickness $\geq$ 5 mm measured by ultrasound may identify an individual with a higher likelihood of having detectable carotid atherosclerosis.[19] More expensive imaging techniques such as MRI and CT have the advantage of measuring fat area and/or volume and quantifying separately EPI, PERI, and total cardiac adipose tissue,[2] but these methods can be expensive and time consuming and, in the case of CT, expose patients to radiation. Ultrasound may be an appealing alternative to these imaging techniques because of its wide availability, low cost, and lack of radiation exposure. The aim of this study was to assess agreement between MRI (area) and

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**Abbreviations**

**BMI** = Body mass index

**CHD** = Coronary heart disease

**CMR** = Cardiac magnetic resonance

**CT** = Computed tomography

**EPI** = Epicardial adipose tissue

**MRI** = Magnetic resonance imaging

**PERI** = Pericardial adipose tissue

ultrasound (thickness) for the measurement of EPI and PERI and its correlation with metabolic parameters.

## METHODS

### Subjects

The patient population under investigation was a subset of subjects who participated in previously published studies,[7,20] selected according to the following criteria: (1) absence of diabetes at enrollment, (2) BMI $< 40$ kg/m$^2$, (3) absence of metabolic or nonmetabolic diseases (except essential hypertension), and (4) no treatment with drugs known to affect glucose tolerance. A subset of subjects enrolled for the metabolic study also agreed to undergo complete rest echocardiography. Thus, the final group was composed of 49 subjects (38 men, 11 women). The study protocol was approved by the institutional review board of the University of Pisa, and each subject gave written informed consent at the time of enrollment.

### Study Design

Subjects underwent (1) measurement of global cardiac function and regional left ventricular function by MRI and echocardiography, (2) quantitation of abdominal subcutaneous and visceral fat and EPI content by MRI, and (3) quantitation of PERI and EPI by echocardiography or MRI (see below). An individual 10-year coronary heart disease (CHD) risk was estimated using the Framingham Heart Study prediction score sheet.[21]

### Anthropometrics Measurements

Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured while the subjects were fasting and wearing only their undergarments. BMI was calculated as body weight divided by height squared and was used as a marker of obesity degree. The ratio of waist circumference to hip circumference was determined by measuring the waist circumference at the narrowest part of the torso and the hip circumference in a horizontal plane at the level of the maximal extension of the buttocks.

### MRI

Abdominal visceral fat and subcutaneous fat depots were measured by MRI, using imaging procedures that have been published previously.[5] Briefly, images were acquired on a GE Signa Excite HD 1.5-T scanner (GE Medical Systems, Milwaukee, WI; slew rate, maximum 150 T/m/sec) that operates with a 50 mT/m gradient using a body coil. A sagittal localizing image was used to center transverse sections on the line through the space between L4 and L5. Thirty-two transverse, T1-weighted 256 × 256 images (repetition time, 135 msec; echo time, 4.2 msec; flip angle, 90°; field of view, 50 cm; pixel size, 1.875 × 1.875 mm) were acquired during a breath hold with a slice thickness of 5 mm and no overlap. Data were transferred to a dedicated workstation and analyzed using software developed ad hoc[22] to determine abdominal subcutaneous and visceral fat areas and volumes. Subcutaneous fat area was analyzed by automatic detection of the outer and inner margins of subcutaneous adipose tissue as a region of interest from the cross-sectional images and by counting the number of pixels between the outer and inner margins of subcutaneous adipose tissue. Visceral (intra-abdominal) fat area was determined using histograms specific to the visceral regions. The histograms were summed over the range of pixel values designated as fat by fitting two normal analysis distribution curves to them. A factor of 0.92 was used to convert adipose tissue volume into adipose tissue mass.[5]

MRI acquisition of the heart involved a standardized protocol. A cardiac coil and electrocardiographic triggering were used for the sequences; during the acquisition time, patients were in breath hold (10–12 sec). Cardiac adipose tissue scans were obtained by fast spin-echo T1-weighted sequences with oblique axial orientation, for a correct study of horizontal long axes of the heart in diastole[23] (echo time, 42 msec; echo train length, 23 msec; bandwidth, 62.50 KHz; slice thickness, 8 mm; slice gap, 0 mm; field of view, 28.5 cm; matrix size, 288 × 224; number of signals acquired, 1; trigger delay, minimum; 8-mm-thick section, 0-mm intersection gap, field of view, and a 256 × 256 matrix). EPI was defined as any adipose tissue located within the pericardial sac.[5,8] PERI and EPI areas were measured using an in-house semiautomatic program to determinate the margin of fat around the heart, identifying region of interest and measuring the number of pixels, as previously described.[5]

### Echocardiography

Each subject underwent transthoracic two-dimensional echocardiography according to the recommendations of the European Association of Echocardiography[24] (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway), with an M3S matrix-array transducer. Echocardiography was performed using standard techniques with subjects in the left lateral decubitus position. Depth was adjusted as the aortic and mitral valves were positioned lowest on the screen. The adipose fat depot was measured on the free wall of the right ventricle from both parasternal long-axis and short-axis views at end-diastole in three cardiac cycles. The maximum value at any site was measured, and the average value was considered.[25] EPI was defined as an echolucent space between the linear echodense parietal pericardium and the right ventricular epicardium, and PERI was defined as an echolucent area above the parietal pericardium. EPI and PERI were measured on the still images of the two-dimensional echocardiogram obtained at end-diastole on both parasternal long-axis and short-axis views, as described previously.[9] Echocardiograms were preliminarily read by a first reader and subsequently reread by a highly experienced reader. Both readers were blinded to subjects' anthropometric features. The coefficient of variation between the two different echocardiographers was 4%, indicating good reproducibility of the echocardiographic measurements.

### Statistical Analysis

Data are expressed as mean ± SEM. Data with a skewed distribution (plasma triglyceride, cholesterol, and insulin concentrations) are expressed as medians and interquartile ranges and were log-transformed for use in statistical analysis. The two methods (echocardiography and MRI) were compared using Bland Altman plots. Given the different units (millimeters vs square millimeters), we normalized the data to the total cardiac fat, calculated as the sum of either extra-PERI and PERI thickness (millimeters) or area (square millimeters). In this way, both methods gave values ranging from 0 and 1.

Insulin sensitivity was calculated as quantitative insulin sensitivity check index and using the oral glucose insulin sensitivity index, which equals the average metabolic clearance rate of glucose during the oral glucose tolerance test and has been validated against the euglycemic insulin clamp technique.[26] Ten-year CHD risk was calculated using the Framingham score.[21] Correlations were calculated using Spearman's coefficient.

## RESULTS

Clinical, echocardiographic, and MRI characteristics of the study population are reported in Table 1. As shown in the table, in this group of subjects with a wide range of BMIs, most cardiac fat was constituted by PERI (77%). In Figure 1, we report two sample cases acquired with MRI and echocardiography.

### Concordance in the Assessment of Cardiac Fat

A good correlation was found between the PERI measurements obtained with the two techniques, but not for EPI (Figure 2). On Bland-Altman analysis, when the EPI and PERI values were normalized to total fat, the agreement between the two techniques was good, with a nonsignificant trend toward overestimation of EPI and underestimation of PERI with echocardiography (Figure 2).

### The Relationship Between Cardiac Fat and Metabolic Parameters

As shown in Table 2, PERI, but not EPI, measured with both techniques was correlated with the parameters of metabolic syndrome such as triglyceride and glucose concentrations, blood pressure, insulin sensitivity, and BMI. PERI thickness on echocardiography showed a strong correlation with 10-year CHD Framingham risk score, whereas no correlation was found with epicardial risk score (Table 2).

### The Relationship Between Cardiac Fat and Visceral Fat

Visceral and abdominal subcutaneous fat volumes were measured using MRI. Both techniques showed a positive association between visceral fat and PERI, but no correlation with EPI depots (Figures 3 and 4). Subcutaneous fat volumes were significantly correlated with both EPI and PERI measured on MRI but not echocardiography. Again, this difference may be accounted for the parameters measured, area versus thickness.

**Table 1** Clinical characteristics of the population

| Variable | Value |
|---|---|
| Men/women | 38/11 |
| NGT/IGT/T2DM | 34/13/1 |
| Age (y) | 48 ± 1 (25–68) |
| BMI (kg/m$^2$) | 28.8 ± 0.5 (21–40) |
| Waist circumference (cm) | 97 ± 2 (68–125) |
| Hip circumference (cm) | 105 ± 1 (80–138) |
| Waist-to-hip ratio | 0.92 ± 0.10 (0.72–1.09) |
| Echocardiographic EPI thickness (mm) | 3.1 ± 0.3 (0.5–8.5) |
| Echocardiographic PERI thickness (mm) | 4.7 ± 0.3 (1–10) |
| MRI EPI area (mm$^2$) | 827 ± 54 (172–2,008) |
| MRI PERI area (mm$^2$) | 1,813 ± 128 (100–4,014) |
| MRI TCAT area (mm$^2$) | 264 ± 152 (467–5,007) |
| SC (kg) | 3.5 ± 0.2 (1.1–8.3) |
| VF (kg) | 1.3 ± 0.1 (0.1–2.6) |
| VF/SC ratio | 0.39 ± 0.3 (0.06–0.86) |
| Triglyceride (mmol/L) | 0.9 (0.8) (0.3–4.0) |
| Cholesterol (mmol/L) | 5.1 (0.9) (2.1–7.6) |
| HDL cholesterol (mmol/L) | 1.2 (0.3) (0.7–2.4) |
| Systolic blood pressure (mm Hg) | 131 ± 2 (100–181) |
| Diastolic blood pressure (mm Hg) | 77 ± 2 (46–102) |
| Glucose (mmol/L) | 5.5 ± 0.1 (4.6–8.2) |
| Insulin (pmol/L) | 72 (45) (16–237) |
| QUICKI | 0.142 ± 0.002 (0.119–0.183) |
| 10-year CHD risk | 7.7 ± 0.8 (2–25) |

*HDL*, High-density lipoprotein; *IGT*, impaired glucose tolerance; *NGT*, normal glucose tolerance; *QUICKI*, quantitative insulin sensitivity check index; *SC*, subcutaneous fat; *TCAT*, total cardiac adipose tissue; *T2DM*, type 2 diabetes mellitus; *VF*, visceral fat.
Data are expressed as numbers, mean ± SEM, or median (interquartile range).

## DISCUSSION

In obese patients, PERI was strongly correlated with the metabolic syndrome, whereas no correlation was found with EPI. In particular, PERI was associated with cardiovascular risk factors, increased visceral fat accumulation, blood pressure, glucose tolerance, lipid concentrations, insulin resistance, and 10-year CHD risk calculated using the Framingham score. Moreover, when comparing ultrasound and cardiac magnetic resonance (CMR) for the detection of total fat and the relative contribution of EPI and PERI, the two techniques provided comparable results. Our results suggest a prevalent role of PERI compared with EPI related to the metabolic syndrome and cardiovascular risk factors in a wide range of obese healthy volunteers. To our knowledge, no report exists on the comparison of ultrasound and CMR for the assessment of cardiac fat and its relation to metabolic syndrome.

### Comparison With Previous Studies

Several clinical studies have shown the relationship of echocardiographic EPI thickness and risk factors. EPI thickness in subjects with the metabolic syndrome is significantly higher than that observed in subjects without the metabolic syndrome.[12] EPI thickness is inversely associated with insulin sensitivity, as assessed by euglycemic hyperinsulinemia clamp studies in obese subjects.[13] Moreover, EPI is independently associated with fasting glucose, low-density lipoprotein cholesterol, and blood pressure.[27] Our results are consistent with these previous results. Although in humans, cardiac fat has been evaluated mainly using ultrasonography, measuring EPI thickness, CMR and CT are able to quantify volumes of cardiac fat and distinguish between EPI and PERI. A recent review showed that the association between metabolic parameters and visceral fat was stronger with total rather than epicardial cardiac fat.[2] In the Framingham Heart Study, PERI measured by CT was correlated with multiple measures of adiposity and cardiovascular disease risk factors. In a large cohort of subjects, PERI measured by CT was found to be predictive of incident CHD independent of conventional risk factors.[8] In a previous study from our group, which measured both PERI and EPI, only PERI area, not EPI, was correlated with visceral fat.[5] Cardiac fat is deposited

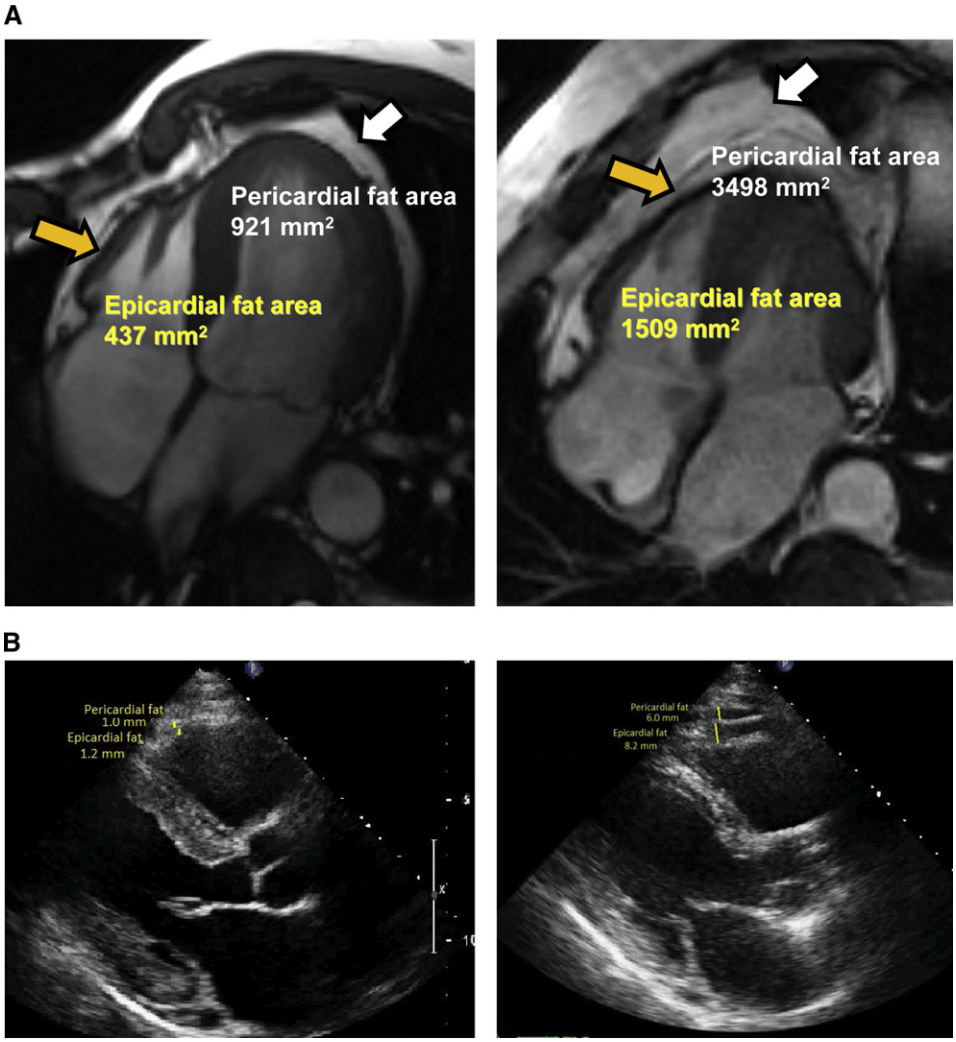


**Figure 1** (*Top*) Four-chamber view of the heart of a subject with low total cardiac fat (*left*) and a subject with high total cardiac fat (*right*). (*Bottom*) Transthoracic long-axis view of the heart of a subject with cardiac (intra-abdominal and PERI) fat (*left*) and cardiac fat (*right*).

both strictly around the myocardium (EPI) but also in the intrathoracic space (PERI or mediastinal fat) and has been found strongly associated with obesity and increased visceral fat.[2,6-9,25]

### Pathophysiologic Implications

In the present study, we measured two different layers of fat, EPI and PERI. There are several reasons to distinguish between these two types of fat with regard to embryonic origin, distribution, function, and vascularization. PERI originates from the primitive thoracic mesenchyme, and it is supplied by noncoronary sources, whereas EPI shares the same microcirculation as the myocardium.[25,27,28] However, under normal conditions, PERI is 20% to 50% of the heart mass, whereas EPI represents approximately 20%. Therefore, they are two different cardiac visceral fat depots. Few studies have addressed the potential different behavior of the two depots. In fact, reports from both the Framingham Heart Study and the Multi-Ethnic Study of Atherosclerosis do not seem to distinguish between these two depots when discussing their biomolecular properties,[8,29] defining PERI as any adipose tissue located within the pericardial sac. Hence, some authors prefer to define PERI as paracardial fat.[30]

The physiologic, biochemical, and biomolecular properties of EPI with its potential interrelation with the myocardium are better characterized than those of PERI, and more studies are needed to explore these differences, if any. The present study provides new insights on PERI (or paracardial fat) and its potential role as a biomarker of risk in obese patients. The reason why, in this study population, the two fat depots behaved differently is a matter of speculation. However, both techniques, ultrasound and CMR, when blindly used provided the same results, with good agreement. Transthoracic echocardiography can be accurately used for the quantitation of cardiac fat, but the quantitation of only EPI is often difficult, highly dependent on the acoustic window and on the operator's experience. Compared with CT, echocardiography is free of ionizing radiation, which is an increasingly important issue from the patient and social perspectives,[31,32] especially in cardiology patients exposed to high cumulative radiation doses from noninvasive testing.[33] However, only with MRI or CT is it possible to quantify the area of cardiac adipose tissue, distinguishing between EPI and extra-PERI, as well as avoiding pericardial fluids (sometimes present even in normal cardiac conditions).

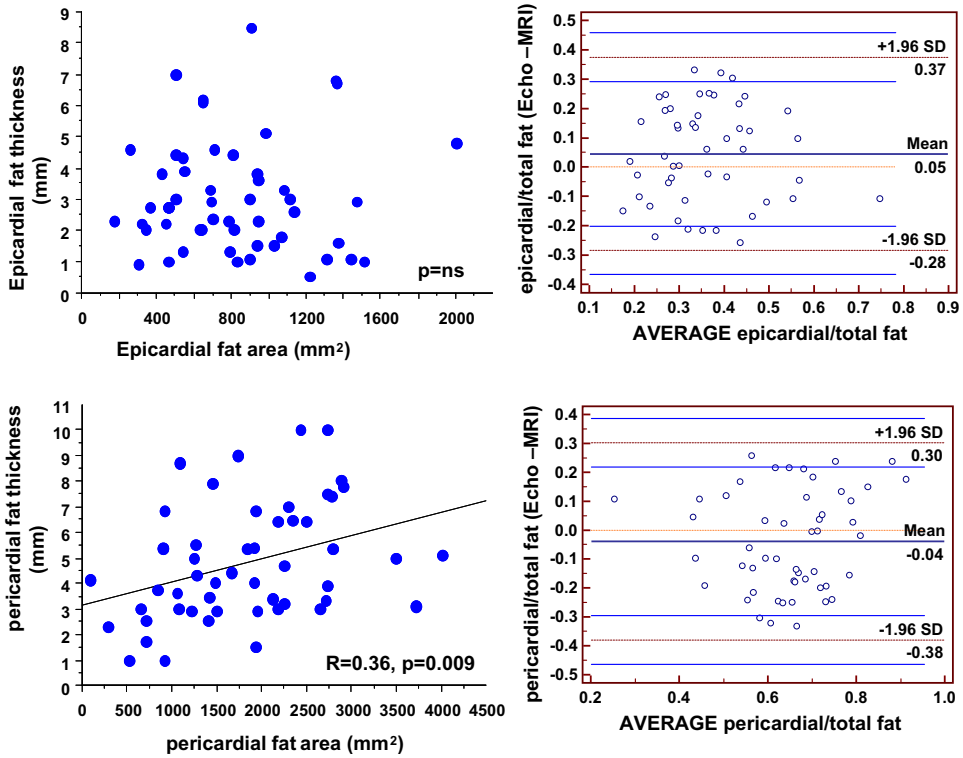


Figure 2 (*Left*) Relationship between fat thickness measured by echocardiography and fat measured by MRI. (*Right*) Bland-Altman plots for the differences between the MRI and echocardiographic data expressed as percentage of total cardiac fat (PERI plus EPI) to compare the two measurements.

Table 2 Matrix of correlations

| Variable | Echocardiographic EPI | Echocardiographic PERI | MRI EPI | MRI PERI | MRI TCAT |
|---|---|---|---|---|---|
| BMI | NS | 0.37 (.008) | 0.38 (.006) | 0.44 (.001) | 0.51 (.0001) |
| Age | 0.32 (.02) | 0.52 (<.0001) | 0.29 (.04) | NS | NS |
| Triglyceride | NS | 0.33 (.02) | NS | 0.55 (.0001) | 0.47 (.0006) |
| Cholesterol | NS | NS | NS | 0.35 (.02) | 0.29 (.04) |
| HDL cholesterol | NS | NS | NS | NS | NS |
| VF | NS | 0.32 (.03) | NS | 0.56 (<.0001) | 0.54 (<.0001) |
| SC | NS | NS | 0.39 (.006) | 0.28 (.05) | 0.37 (.009) |
| Systolic blood pressure | NS | 0.37 (.009) | NS | 0.35 (.01) | 0.31 (.3) |
| Diastolic blood pressure | NS | 0.41 (.003) | NS | 0.31 (.3) | 0.32 (.3) |
| Glucose | NS | 0.49 (.003) | NS | 0.27 (.06) | 0.29 (.05) |
| Insulin | NS | NS | NS | NS | NS |
| QUICKI | NS | −0.30 (.04) | NS | −0.26 (.08) | −0.26 (.08) |
| Waist circumference | NS | NS | 0.34 (.02) | 0.51 (.0002) | 0.56 (.0001) |
| Hip circumference | NS | NS | 0.32 (.3) | 0.37 (.01) | 0.43 (.003) |
| 10-year CHD risk | NS | 0.51 (.0001) | NS | 0.35 (.01) | 0.34 (.02) |

*HDL*, High-density lipoprotein; *QUICKI*, quantitative insulin sensitivity check index; *SC*, subcutaneous fat; *TCAT*, total cardiac adipose tissue; *VF*, visceral fat.
Data are expressed as correlation coefficient (*P* value).

## Study Limitations

There were several limitations to be acknowledged in the present study. Two different techniques were directly compared by looking at the contribution of EPI and PERI to total fat (i.e., the ratios EPI/[EPI + PERI] and PERI/[EPI + PERI]), because the two methods give very different measurements (thickness vs area). The Bland-Altman plots showed good agreement between MRI and echocardiography, although a nonsignificant trend toward overestimation of EPI and underestimation of PERI using echocardiography was observed. Moreover, echocardiographic fat thickness assessment has in general higher variability than area measured with MRI, even though highly trained echocardiographers were involved, and all were trained by the same operator, who reviewed all the exams. There is no consensus on methodology for fat assessment,

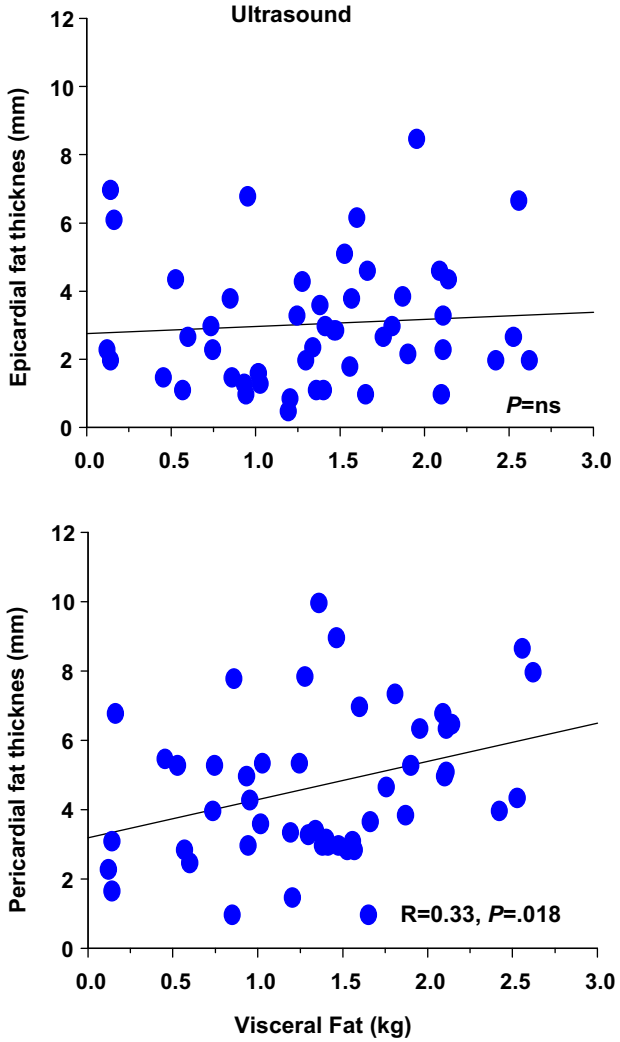


Figure 3 Relationship between visceral fat volume and EPI (*closed circles*) or PERI (*open circles*) measured as fat thickness by echocardiography.

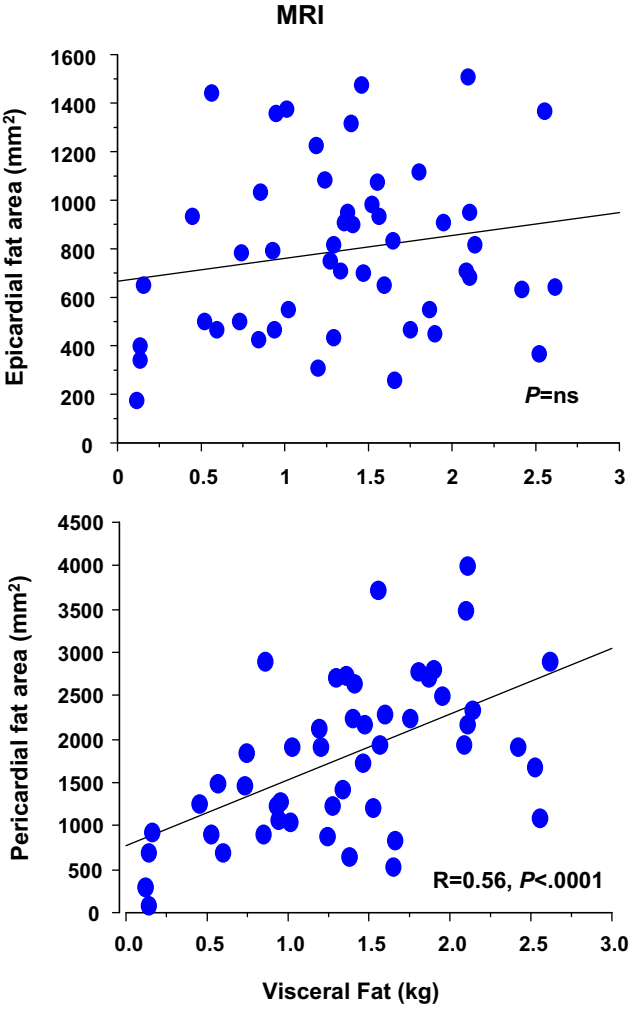


Figure 4 Relationship between visceral fat volume and EPI (*closed circles*) or PERI (*open circles*) measured as fat area by MRI.

but most studies have measured it in end-systole. During diastole, the fat is compressed, so it is best measured at end-systole at the point on the free wall of the right ventricle, at which the ultrasound beam is oriented in a perpendicular manner, with the aortic annulus as a landmark. Conversely, it has been suggested that deformity of EPI also exists during systole and that EPI should be measured in diastole. Because no consensus exists on how to measure cardiac fat with ultrasound, to be consistent with MRI, we measured fat in diastole. Moreover, echocardiography is highly affected by the acoustic window, which may be suboptimal in obese patients. Still, the parasternal views may be accessible in these patients.

The sample size was small, and no definitive conclusions can be drawn, but the patient population under investigation had unique features: all patients were obese in different stages of severity, and all had a thorough metabolic characterization. Moreover, we were able to compare a high-technology imaging technique with a more accessible, low-cost, and readily available one, showing the potential relevant clinical implications of such an approach.

## CONCLUSIONS

Imaging of cardiac fat has relevant implications for the assessment of risk in several subsets of patients.[2,6,10,12] Our results demonstrate that MRI and ultrasound are comparable for the assessment of adipose tissue, with differences strictly related to technology characteristics: MRI was more accurate and operator independent than echocardiography and not limited by the acoustic window, but with threefold higher cost, lower availability, and longer imaging and analysis times. PERI is significantly related to the metabolic syndrome, more so than EPI, but the relation between cardiac fat depots and metabolism is still elusive, and more studies on several subsets of patients are warranted. Moreover, which technique and which parameter (i.e., EPI vs PERI or rather increased deposition fat around the heart) is best to be translated into clinical practice have yet to be determined.

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